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Synthesis of a group of 1*H*-benzimidazoles and their screening for antiinflammatory activity

D Evans[1], TA Hicks[1], WRN Williamson[1]*, W Dawson[2], SCR Meacock[2], EA Kitchen[2]

[1]*Organic Chemistry Department, Lilly Research Centre, Ltd;*
[2]*Biology Department, Lilly Research Centre, Ltd, Eli Lilly & Company, Erl Wood Manor, Windlesham, Surrey, GU20 6PH, UK*

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substituted 1*H*-benzimidazole / anti-inflammatory activity

Introduction

Before the work described herein was undertaken anti-inflammatory activity in 1*H*-benzimidazoles has been reported in the literature. The compounds consisted mainly of 1*H*-benzimidazoles with fairly simple substituents. Amongst the compounds were 'dibazol', 2-benzyl-1*H*-benzimidazole [1], 2-(3-fluorophenyl)-1*H*-benzimidazole [2], 2-(4-thiazolyl)-1*H*-benzimidazole [3] and 2-[(4-chlorophenyl)methyl]-5-trifluoromethyl-1*H*-benzimidazole [4]. Compounds in which the benzimidazole nitrogen atom was substituted included 1-[(4-fluorophenyl)methyl]-2-([(4-propyl-1-piperazinyl)methyl]-1*H*-benzimidazole [5]. 1*H*-Benzimidazole and simple derivatives of it had also been claimed to prevent stomach damage caused by inflammation inhibitors [6]. In this paper we describe the synthesis and testing in the rat adjuvant arthritis screen [7] of a number of substituted benzimidazoles (tables I and II, compounds **1–72**). The structures of these compounds were chosen so that the compounds would include weakly basic, weakly acidic and neutral molecules.

Chemistry

The 1*H*-benzimidazoles described here were prepared by conventional methods from appropriate intermediates. The majority of the benzimidazoles were substituted with either methyl or phenyl in the 1-position, and 2-(4-chlorophenyl) in the 2-position. The fixing of substitution in the 1-position ensured that substituents in the benzene nucleus of the 1*H*-benzamidazoles would be in unambiguous positions. The 1*H*-benzamidazoles prepared are listed in tables I and II. Intermediates which were novel (largely unisolated) compounds are listed in table III. Further details of preparative procedures are given in the *Experimental protocols*; methods are numbered in order and are referred to in the tables as necessary for other similar preparation.

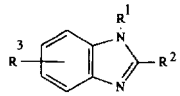
The intermediate **76** when reacted with diethylamine gave the ether **36** or the amine **38**, when methanol (for **36**) or dichloromethane or toluene (for **38**) were the respective reaction solvents. In the case of the condensation products **65–69**, although the method of preparation was the same for each compound, the *E*/*Z* ratio of the double bonds varied from 100% *Z* (**69**) to 50% (**66** and **67**).

Results and discussion

The compounds **1–72** (tables I and II) were assessed on the rat adjuvant arthritis screen [7]. Indomethacin was used as a control compound. The results for the nine compounds **1**, **2**, **18**, **36**, **47**, **54**, **55**, **57** and **61** which gave 30% or greater reduction in non-injected paw volume compared to controls (parameter C), together with the results for indomethacin, are given in table IV. Only two of the compounds (**36** and **47**) showed moderately good activity on the joint mobility

*Present address: Littlecote, One Pin Lane, Farnham Common, Buckinghamshire, SL2 3RA, UK

Table I. 1*H*-Benzimidazoles.



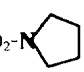
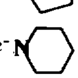
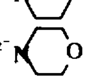
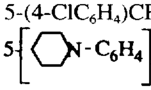
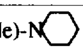
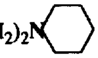
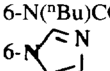
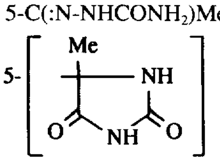
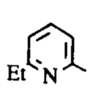
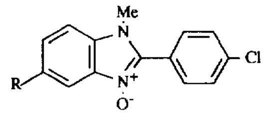
Compound	*R¹*	*R²*	*R³*	*Yield (%)*	*Mp (°C)*	*Cryst solvent*	*Analysis*	*Method*
1	H	4-ClC_6H_4	5(6)-MeO	62	222	$COMe_2$	$C_{14}H_{11}ClN_2O$ (C, H, N)	1
2	H	4-ClC_6H_4	5(6)-HO	70	284–288	$CHCl_3$/MeOH	$C_{13}H_9ClN_2O$ (C, H, N)	2
3	H	4-ClC_6H_4	4(7)-EtO	52	292–294	EtOH/H_2O	$C_{15}H_{13}ClN_2O$ (C, H, N)	3
4	H	4-ClC_6H_4	4(7)-HO	86	265–268	EtOH/H_2O	$C_{13}H_9ClN_2O$ (C, H, N)	4
5	Me	4-ClC_6H_4	7-OEt	16	96	Cyclohexane	$C_{16}H_{15}ClN_2O$ (C, H, N)	1
6	Me	4-ClC_6H_4	7-OH	55	230–232	MeOH	$C_{14}H_{11}ClN_2O$ (C, H, N)	4
7	Me	4-ClC_6H_4	5-MeO, HCl, 0.5H_2O	79	215	Dioxan/EtOH/4NHCl	$C_{15}H_{13}ClN_2O$•HCl•0.5H_2O (C, H, N)	1
8	Me	4-ClC_6H_4	5-OH	19	185–188	MeOH/H_2O	$C_{14}H_{11}ClN_2O$ (C, H, N)	2
9	Me	4-ClC_6H_4	5-(4-Cl-C_6H_4CO)O-	71	198–200	Pptd with H_2O	$C_{21}H_{14}Cl_2N_2O_2$ (C, H, N)	5
10	Me	4-ClC_6H_4	5-(2-NO_2-4-F-C_6H_3)O-	45	148.5–149.5	MeOH	$C_{20}H_{13}ClFN_3O_3$ (C, H, N)	6
11	Me	4-ClC_6H_4	5-(2-NO_2-C_6H_4)O-, HCl, 0.5H_2O	8	212–215	HCl/MeOH	$C_{20}H_{14}ClN_3O_3$•HCl•0.5H_2O (C, H, N)	6
12	Me	4-ClC_6H_4	5-O-Et	80	138–140	EtOH/H_2O	$C_{16}H_{15}ClN_2O$ (C, H, N)	6
13	Me	4-ClC_6H_4	5-O-*n*Pr	29	122–123	C_6H_5Me	$C_{17}H_{17}ClN_2O$ (C, H, N)	6
14	Me	4-ClC_6H_4	5-O-$(CH_2)_2$OH	18	174–175	aq MeOH	$C_{16}H_{15}ClN_2O_2$ (C, H, N)	6
15	Me	4-ClC_6H_4	5-O-$(CH_2)_3$OH	57	139–140	C_6H_5Me	$C_{17}H_{17}ClN_2O_2$ (C, H, N)	6
16	Me	4-ClC_6H_4	5-O-$(CH_2)_2NEt_2$	32	77–82.5	Pptd from HCl using aq NH_3	$C_{20}H_{24}ClN_3O$ (C, H, N)	6
17	Me	4-ClC_6H_4	5-O-$(CH_2)_2$- 	19	129–130	EtOAc/C_6H_5Me	$C_{20}H_{22}ClN_3O$ (C, H, N, Cl)	6
18	Me	4-ClC_6H_4	5-O-$(CH_2)_2$- 	37	108–109	pet[a]/EtOAc	$C_{21}H_{24}ClN_3O$ (C, H, N)	6
19	Me	4-ClC_6H_4	5-O-$(CH_2)_2$- 	76	115–116	aq DMSO	$C_{20}H_{22}ClFN_3O_2$ (C, H, N)	6
20	Me	4-ClC_6H_4	5-O-$(CH_2)_2$-NMe_2	14	131–132	pet/EtOAc	$C_{18}H_{20}ClN_3O$ (C, H, N)	6
21	Me	4-ClC_6H_4	5-O-$(CH_2)_3$-NMe_2	37	99–100	pet/C_6H_5Me	$C_{19}H_{22}ClN_3O$ (C, H, N)	6
22	Me	4-ClC_6H_4	5-O-CH(Me)CH_2NMe_2	42	89–90	Et_2O/MeOH/pet	$C_{19}H_{22}ClN_3O$ (C, H, N)	6
23[b]	Me	4-ClC_6H_4	5-NO_2	27	207–209[c]	EtOH/EtOAc/H_2O	$C_{14}H_{10}ClN_3O_2$ (C, H, N)	[11]
24[b]	Me	4-ClC_6H_4	5-NH_2 (tartrate, 1.5H_2O)	3	170–171[d]	EtOH	$C_{18}H_{18}ClN_3O_6$•HCl•1.5H_2O (C, H, N)	[12]
25[b]	Me	4-ClC_6H_4	5-$N^+Me_3I^-$	38	197–198	MeOH	$C_{17}H_{19}ClIN_3$ (C, H,Cl, N, I)	7
26	Me	4-ClC_6H_4	5-$NHCOCF_3$	95	268	Pptd H_2O	$C_{16}H_{11}ClF_3N_3O$ (C, H, N)	8
27[b]	Me	4-ClC_6H_4	5-$NHSO_2C_6H_4$-4-Me	48	224–225	EtOH/DMF	$C_{21}H_{18}ClN_3O_2S$ (C, H, N)	5
28[c]	Me	4-ClC_6H_4	5-(4-ClC_6H_4)CH:N-	74	196.5–198	MeOH/$CHCl_3$	$C_{21}H_{15}Cl_2N_3$ (C, H, N)	9
29	Me	4-ClC_6H_4	5-  CH:N-	63	195–197	EtOAc	$C_{26}H_{25}ClN_4$ (C, H, N)	9
30[c]	Me	4-ClC_6H_4	5-(4-F-2-NO_2-C_6H_3)NH-	28	200–201	$CHCl_3$/MeOH	$C_{20}H_{14}ClFN_4O_2$ (C, H, N)	6
31	Me	4-ClC_6H_4	5-CH:CH_2	62	104–106	PhMe/pet	$C_{16}H_{13}ClN_2$ (C, H, N, Cl)	10
32	Me	4-ClC_6H_4	5-Et	39	121–123	EtOAc	$C_{16}H_{15}ClN_2$ (C, H, N, Cl)	11
33	Me	4-ClC_6H_4	5-Cl	35	133–135	MeOH-Et_2O	$C_{14}H_{10}Cl_2N_2$ (C, H, N)	12
34	Me	4-ClC_6H_4	5-COMe	62	163	EtOAc	$C_{16}H_{13}ClN_2O$ (C, H, N)	1
35	Me	4-ClC_6H_4	5-CH(OH)Me	63	169–170	EtOH	$C_{16}H_{15}ClN_2O$ (C, H, N)	13
36	Me	4-ClC_6H_4	5-CH(OMe)Me	62	126.5–127.5	PhMe/pet	$C_{17}H_{17}ClN_2O$ (C, H, N)	14
37	Me	4-ClC_6H_4	5-C(:NOH)Me	55	283–284	DMF/H_2O	$C_{16}H_{14}ClN_3O$ (C, H, N)	15
38	Me	4-ClC_6H_4	5-CH(NEt_2)Me, 1.5H_2O	48	78–81	PhMe/pet	$C_{20}H_{24}ClN_3$•1.5H_2O (C, H, N)	16

Table I. *(Continued)*

Compound	*R¹*	*R²*	*R³*	*Yield (%)*	*Mp (°C)*	*Cryst solvent*	*Analysis*	*Method*
39	Me	4-ClC_6H_4	5-CH(Me)-	40	110–112	Et_2O	$C_{21}H_{24}ClN_3$ (C, H, N)	16
40	Me	4-ClC_6H_4	5-CH($NHCOCH_3$)Me	36	174.5–175.5	EtOAc/EtOH	$C_{18}H_{18}ClN_3O$ (C, H, N)	17
41	$(CH_2)_3NH_2$	H	H (maleate salt)	67	140–141	EtOH	$C_{14}H_{17}N_3O_4$ (C, H, N)	18
42	$(CH_2)_2OH$	4-ClC_6H_4	6-Cl	45	196–198	EtOH/H_2O	$C_{15}H_{12}Cl_2N_2O$ (C, H, N, Cl)	19
43	C_6H_5	4-ClC_6H_4	6-Cl	13	197–198	EtOH	$C_{19}H_{12}Cl_2N_2$ (C, H, N)	20
44	C_6H_5	4-ClC_6H_4	6-OMe	59	171–172.5	EtOH	$C_{20}H_{15}ClN_2O$ (C, H, N)	20
45	C_6H_5	4-ClC_6H_4	6-OH, 0.6H_2O	43	254–255	EtOH	$C_{19}H_{13}ClN_2O$•0.6H_2O (C, H, N)	2
46	C_6H_5	4-ClC_6H_4	6-$O(CH_2)_3OH$	57	188	EtOH	$C_{22}H_{19}ClN_2O_2$ (C, H, N)	6
47	C_6H_5	4-ClC_6H_4	6-$O(CH_2)_2NEt_2$, 2HCl, 2.3H_2O	34	210	MeOH/conc HCl	$C_{25}H_{26}ClN_3O$•2HCl, 2.3H_2O (C, H, N)	6
48	C_6H_5	4-ClC_6H_4	6-$O(CH_2)_2$	35	138–140	CH_2Cl_2	$C_{26}H_{26}ClN_3O$ (C, H, N)	6
49	C_6H_5	4-ClC_6H_4	6-$O(CH_2)_3NMe_2$	54	126	pet	$C_{24}H_{24}ClN_3O$ (C, H, N)	6
50	C_6H_5	4-$MeOC_6H_4$	6-OMe	59	192	EtOH	$C_{21}H_{18}N_2O_2$ (C, H, N)	20
51	C_6H_5	4-HOC_6H_4	6-OH, HCl, H_2O	82	212 (dec)	H_2O[e]	$C_{19}H_{14}N_2O_2$•HCl, H_2O (C, H, N)	2
52	C_6H_5	4-[4-Et_2N-$(CH_2)_2O$]C_6H_4	6-$O(CH_2)_2NEt_2$	16	306 (0.2)	–	$C_{31}H_{40}N_4O_2$ (C, H, N)	6 [cf 9]
53	C_6H_5	4-ClC_6H_4	5-NO_2	16.5	208	EtOH	$C_{19}H_{12}ClN_3O_2$ (C, H, N)	20
54	C_6H_5	4-ClC_6H_4	6-$NH(CH_2)_2OH$	24	225	EtOH	$C_{21}H_{18}ClN_3O$ (C, H, N)	19
55	C_6H_5	4-ClC_6H_4	6-$NH(CH_2)_3Me$	39	158	EtOH	$C_{23}H_{22}ClN_3$ (C, H, Cl, N)	33(ii)
56	C_6H_5	4-ClC_6H_4	6-N(^{n}Bu)$COCHMe_2$	40	213–210 (0.09)	–	$C_{27}H_{28}ClN_3O$ (C, H, N)	21
57	C_6H_5	4-ClC_6H_4	6-	32	223	EtOAc	$C_{22}H_{15}ClN_4$ (C, H, N)	20
58	C_6H_5	4-ClC_6H_4	5-COMe	31	159	EtOH	$C_{21}H_{15}ClN_2O$ (C, H, Cl, N)	19
59	C_6H_5	4-ClC_6H_4	5-CH(OH)Me	97	165	EtOH/H_2O	$C_{21}H_{17}ClN_2O$ (C, H, Cl, N)	13
60	C_6H_5	4-ClC_6H_4	5-COCH:NOH	14	231 (dec)	EtOAc	$C_{21}H_{14}ClN_3O_2$ (C, H, Cl, N)	22
61	C_6H_5	4-ClC_6H_4	5-CH(NH_2)Me (maleate salt)	36	206	EtOH	$C_{25}H_{22}ClN_3O_4$ (C, H, Cl, N)	23
62	C_6H_5	4-ClC_6H_4	5-CH(NHEt)Me (maleate salt)	37	228	EtOH	$C_{27}H_{26}ClN_3O_4$ (C, H, Cl, N)	23 [15]
63	C_6H_5	4-ClC_6H_4	5-C(:N-$NHCONH_2$)Me	96	249	H_2O	$C_{22}H_{18}ClN_5O$ (C, H, Cl, N)	24
64	C_6H_5	4-ClC_6H_4	5-	73	205	EtOH	$C_{23}H_{17}ClN_4O_2$ (C, H, Cl, N)	25
65	C_6H_5	4-ClC_6H_4	5-COCH:CHC_6H_5 (85:15 *E,Z* mixture)	49	198	EtOH	$C_{28}H_{19}ClN_2O$ (C, H, Cl, N)	26
66	C_6H_5	4-ClC_6H_4	5-COCH:CHC_6H_4-4-Cl (1:1 *E,Z* mixture)	53	218–219	EtOH	$C_{28}H_{18}Cl_2N_2O$ (C, H, Cl, N)	26
67	C_6H_5	4-ClC_6H_4	5-COCH:CHC_6H_3-3,4-Cl_2 (1:1 *E,Z* mixture)	38	166	EtOAc	$C_{28}H_{17}Cl_3N_2O$ (C, H, N)	26
68	C_6H_5	4-ClC_6H_4	5-COCH:CHC_6H_4-4-OMe (84:16 mixture)	36	193	EtOH	$C_{29}H_{21}ClN_2O_2$ (C, H, N)	26
69	C_6H_5	4-ClC_6H_4	5-COCH:CHC_6H_4-4-Me (*E* only)	24	184	EtOAc	$C_{29}H_{21}ClN_2O$ (C, H, N)	26
70	H		H [8]	50	171–173	C_6H_5Me	$C_{14}H_{13}N_3$ (C, H, N)	27

[a]Pet refers to light petroleum of bp 40–60 °C. [b]Mutagenic compound. [c]Literature quotes mp 197–199 °C. [d]Literature quotes mp 125 °C for free base. [e]Precipitated from Na salt solution by hydrochloric acid.

Table II. 1*H*-Benzimidazole N-oxides.



Compound	*R*	*Yield (%)*	*Mp (°C)*	*Cryst solvent*	*Analysis*	*Method*
71	OH	14	248–250	EtOH/Me_2CHOH	$C_{14}H_{11}ClN_2O_2$ (C, H, N, O)	2
72	$O(CH_2)_2$-N(morpholino)O·$1.25H_2O$	16	155–157	C_6H_5Me	$C_{20}H_{22}ClN_3O_3$·$1.25H_2O$ (C, H, N, O)	6

parameter J, and these compounds, along with **1**, **55** and **57** showed moderately good activity on the C secondary lesion. No correlation between activities on the C and J parameters and the acidity, basicity and neutrality of the compounds was evident.

Experimental protocols

Chemistry

Melting points were determined using either Kofler hot stage or Kofler calibrated hot bench equipment and are uncorrected. The structures of all the compounds were checked by IR, UV, NMR and mass spectra. Elemental microanalyses were within ±0.4% of the calculated values and were determined by G Maciak and associates, Lilly Research Laboratories, Indianapolis. Mutagenicity testing was also carried out in these laboratories. Illustrative methods are given as follows.

*Method 1. 2-5-Chlorophenyl)-5(6)-methoxy-1H-benzamidazole **1***
The amide **73** (14 g, 0.054 mol) in 4 M HCl (175 mL), dioxan (35 mL) and EtOH (35 mL) was refluxed for 3 h [10]. The mixture was diluted with H_2O (600 mL), the filtered solid treated with conc aq NH_3 (35 mL) and extracted with EtOAc. The extracted product was recrystallized. (The NH_3 treatment was omitted when the hydrochloride was isolated.)

*Method 2. 2-(4-Chlorophenyl)-5(6)-hydroxy-1H-benzimidazole **2***
The benzimidazole **1** (15 g, 0.058 mol) was stirred and refluxed in AcOH (150 mL) and 48% HBr (150 mL) for 8.75 h. The mixture was diluted with H_2O (600 mL), the solid was filtered, treated with conc NH_3 solution (75 mL) in H_2O (150 mL) and the product extracted with EtOAc. The dried ($MgSO_4$) EtOAc solution (750 mL) was treated with light petroleum (bp 40–60 °C), and the precipitated product was filtered off and recrystallized. When this reaction was repeated on a larger scale the *N*-oxide **71** was isolated.

*Method 3. 2-(4-Chlorophenyl)-4(7)-ethoxy-1H-benzimidazole **3***
4-Chlorobenzimidoethyl ether hydrochloride (10.08 g, 0.046 mol) was added to a solution in EtOH (50 mL) of 1,2-diamino-3-ethoxybenzene (0.046 mol, produced by catalytic hydrogenation of 1,3-dinitro-3-ethoxybenzene, 9.79 g, 0.046 mol) and the solution was stirred and refluxed for 2 h under N_2. The solution was cooled in ice and the crystalline product **3** filtered, washed with EtOH/H_2O (20:10 mL) and dried.

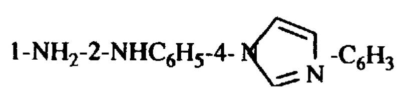
*Method 4. 2-(4-Chlorophenyl)-4-(7)-hydroxy-1H-benzimidazole **4***
The ethoxybenzimidazole **3** (3 g, 0.011 mol) in CH_2Cl_2 (30 mL) was stirred for 2.5 h with BBr_3 (7.9 g, 3 mL, 0.03 mol). The mixture was cooled in an ice-bath and cautiously treated with saturated $NaHCO_3$ solution (100 mL) and stirred for 1 h. The resulting solid was filtered off, treated with H_2O (100 mL), EtOAc (300 mL) and saturated $NaHCO_3$ (150 mL). The EtOAc was washed with H_2O, dried ($MgSO_4$), filtered and evaporated and the product crystallized.

*Method 5. 5-(4-Chlorobenzoyloxy)-2-(4-chlorophenyl)-1-methyl-1H-benzimidazole **9***
The hydroxy benzimidazole **8** (10 g, 0.039 mol) in pyridine (50 mL) was treated with 4-chlorobenzoyl chloride (8 g, 5.8 mL, 0.046 mol), stirred for 15 min at ambient temperature for 1.5 h and kept at ambient temperature for 17 h. The white product was filtered off, treated with H_2O and with saturated $NaHCO_3$ solution (80 mL), filtered, washed with H_2O and dried to give **9**.

*Method 6. 5-(2-Nitro-4-fluorophenyloxy)-2-(4-chlorophenyl)-1-methyl-1H-benzimidazole **10***
Compound **8** (7 g, 0.027 mol), 2,5-difluoronitrobenzene (4.3 g, 0.077 mol), anhydrous K_2CO_3 (3.73 g, 0.027 mol) were heated and stirred in dry dimethylsulfoxide (55 mL) at ca 95 °C for 6.7 h. The mixture was poured into H_2O (275 mL), extracted with EtOAc (3 × 200 mL), then washed with H_2O, and evaporated to dryness to give **10**. (For compounds **12** and **13**, $COMe_2$/MeOH and MeOH respectively were used as reaction solvents; for compounds **14–22** and **46**, NaOH was used instead of K_2CO_3; KOH was used as base and C_6H_5Me as solvent for **47–49** and **52**.)

*Method 7. N-[2-(4-Chlorophenyl)-1-methyl-5-1H-benzimidazolyl]-N,N-dimethyl methanaminium iodide **25***
The amide **26** (9.4 g, 0.02 mol) suspended in dry $COMe_2$ (140 mL) was treated with MeI (22.75 g, 10 mL, 0.16 mol) and powdered NaOH (8 g, 0.2 mol). The mixture was refluxed for 14 min, further MeI (10 mL) and then H_2O (84 mL) was added, and the mixture was refluxed again for 44 min. The clear solution was evaporated in vacuo to give a suspension of ca 100 mL in volume. Water (100 mL) was added and the resulting solid was filtered, washed with H_2O (100 mL), dried at 65 °C/vac and recrystallized.

Table III. Intermediates for compounds of tables I and II.

Compound	*Reference no in tables I and II*	*Structure*	*Yield (%)*	*Mp (°C)*	*Cryst solvent*	*Analysis*	*Method*
73	1	3-NH_2-4-(4-ClC_6H_4CONH)-1-MeO-C_6H_3	95	149	Dioxan/H_2O	$C_{14}H_{13}ClN_2O_2$ (C, H, N)	28
74	5	3-NH_2-2-(4-ClC_6H_4CONMe)-1-EtO-C_6H_3	74	139.5	EtOH	$C_{16}H_{17}ClN_2O_2$[a]	29
75	7	3-NH_2-4-(4-ClC_6H_4CONMe)-1-MeO-C_6H_3	95	105	Dioxan	$C_{15}H_{15}ClN_2O_2$[a]	30
76	31, 36, 38	1-Me-2-(4-ClC_6H_4)-5-(1-ClEt)-benzimidazole, HCl	[b]	Solid	CH_2Cl_2	$C_{16}H_{15}Cl_3N_2$[a]	31
77	34	3-NH_2-4-[4-ClC_6H_4CON(Me)]-1-AcC_6H_3 3-NH(4-ClC_6H_4CO)-4-[NH(Me)]-1-AcC_6H_3	(mixture)	(Oil)	–	$C_{16}H_{15}ClN_2O_2$[a]	28(i)
78	42	2-NH_2-5-Cl-1-[HO$(CH_2)_2$NH]C_6H_3	85	102	H_2O	$C_8H_{11}N_2O$[a]	32
79	54	1-NH_2-2-NHC_6H_5-4-[HO$(CH_2)_2$-NH]C_6H_3	[b]		–	$C_{14}H_{17}N_3O$[a]	33
80	55	1-NH_2-2-NHC_6H_5-4-[NH(nBu)]-C_6H_3	[b]		–	$C_{16}H_{21}N_3$[a]	34
81	57		[b]		ETOAc	$C_{15}H_{14}N_4$[a]	35

[a]Not analysed for elements; [b]yield not determined, as the product was used directly in the next reaction.

Table IV. Adjuvant arthritis results.

Compound number (as in table I)	*Dose (mg/kg)*	*A*	*B*	*C*	*J*
1	33	0	48	43	2
2	33	0	45	31	4
18	33	0	30	30	6
36	33	15	52	48	33
47	33	21	26	46	43
54	33	2	0	35	10
55	33	0	24	42	2
57	33	17	0	51	0
61	33	7	9	33	21
Indomethacin	3	27	84	81	59

Adjuvant arthritis: A = right primary lesion, % reduction in injected paw volume compared to controls, measured from day 0–8; B = right secondary lesion, % reduction in injected paw volume compared to controls, measured from day 9–18; C = left secondary lesion, % reduction in non-injected paw volume compared to controls, measured from day 9–18; J = percentage improvement in joint of the paw, compared to controls.

Method 8. N-[2-(4-Chlorophenyl)-1-methyl-5-1H-benzimidazolyl]trifluoroacetamide ***26***
The amine **24** (as free base, 15.42 g, 0.06 mol) was stirred in CF_3CO_2H (45 mL) with addition of $(CF_3CO)_2O$ (33.6 mL, 0.24 mol) over 11 min then the solution was stirred at room temperature overnight. Water (200 mL) was added to give a product (21.87 g) which was the CF_3CO_2H salt of **26**, $C_{18}H_{12}ClF_6N_3O_3$ (C, H, N). The salt (5 g, 0.011 mol) was shaken in H_2O (20 mL) and $COMe_2$ (175 mL) with NaOH (0.43 g, 0.011 mol), and the $COMe_2$ was removed at 30 °C in vacuo. The residual suspension was diluted with H_2O (50 mL), filtered, washed H_2O (6 × 5 mL) and dried.

Method 9. 2-(4-Chlorophenyl)-5-(4-chlorophenylmethyleneimino)-1-methyl-1H-benzimidazole ***28***
4-Chlorobenzaldehyde (3.4 g, 0.024 mol) was added to a warm solution of the amine (5.2 g, 0.02 mol) in EtOH (40 mL) and shaken. After 1 h the solid was filtered, washed with EtOH and recrystallized.

Method 10. 2-(4-Chlorophenyl)-5-ethenyl-1-methyl-1H-benzimidazole ***31***
Compound **76** (8 g, 0.023 mol) was stirred in refluxing xylene (80 mL) under N_2 for 7 h, and kept at room temperature for 48 h. A small amount of solid was filtered off and the filtrate diluted with light petroleum (bp 40–60 °C, 200 mL) and the resulting solid was recrystallized.

Method 11. 2-(4-Chlorophenyl)-5-ethyl-1-methyl-1H-benzimidazole ***32***
Compound **31** (1.7 g, 0.0063 mol) was hydrogenated for 40 min in EtOH (20 mL) over PtO_2 (0.1 g) in a Parr hydrogenator at 46 psi, the catalyst filtered off, the solvent evaporated and the residue recrystallized.

Method 12. 5-Chloro-2-(4-chlorophenyl)-1-methyl-1H-benzimidazole ***33***
Compound **24** (as free amine, 10.32 g, 0.04 mol) suspended in H_2O (140 mL) and conc HCl (50 mL) was stirred and cooled to –5 °C and treated with a solution of $NaNO_2$ (3.7 g, 0.052 mol) in H_2O (40 mL) dropwise over 42 min. After stirring at 5 °C for 10 min the solution was added to $CuCl_2{\cdot}2H_2O$ (11.12 g, 0.064 mol) in H_2O (150 mL) over 1 min at 10 °C. Cu_2O (5.56 g, 0.04 mol), was added portionwise with stirring over 11 min. The mixture was stirred at ambient temperature for 65 min. The product was filtered, extracted for 12 h with boiling EtOAc in a Soxhlet apparatus, then the resulting residue was shaken with EtOAc and aq NH_3 (d = 0.88). The EtOAc extracts were separated from the aqueous phase, combined with the previous EtOAc extract, dried and evaporated to give a product which was purified by chromatography on basic Al_2O_3 (activity 1) using $CHCl_3$ as eluent, and then recrystallized.

Method 13. 2-(4-Chlorophenyl)-1-methyl-5-(1-hydroxyethyl)-1H-benzimidazole ***35***
The ketone **34** (19 g, 0.067 mol) in EtOH (950 mL) and 2 N NaOH (11 mL) was stirred and treated with a suspension of $NaBH_4$ (23.18 g, 0.6 mol) in EtOH (570 mL) containing 2 N NaOH (11 mL). The mixture was stirred at ambient temperature for 3.3 h. Water (5 L) was added, then the mixture was stirred for 1.75 h and kept at room temperature overnight. The product was filtered off, washed with H_2O and recrystallized.

Method 14. 2-(4-Chlorophenyl)-1-methyl-5-(1-methoxyethyl)-1H-benzimidazole ***36***
The chlorocompound **76** (6 g, 87.8% pure, 0.015 mol) in MeOH (30 mL) was treated with NEt_2 (2.25 g, 0.031 mol, 3.2 mL) and kept at ambient temperature for 2 h. The solution was evaporated at 46 °C/10 mmHg and the residue shaken in EtOAc (50 mL) with aq Na_2CO_3 solution (50 mL). The EtOAc was dried ($MgSO_4$), filtered and evaporated and the product recrystallized.

Method 15. 1-[2-(4-Chlorophenyl)-1-methyl-1H-benzimidazol-5-yl]-1-hydroxyimino ethane ***37***
Sodium hydroxide (3.67 g, 0.092 mol) was added portionwise with stirring over 5 min to a suspension of the ketone **34** (5.22 g, 0.018 mol) and $NH_2OH{\cdot}HCl$ (2 g, 0.029 mol) in EtOH (20.1 mL) and H_2O (1.3 mL). The mixture was stirred at ambient temperature for 16 h, then poured into H_2O (70 mL) containing conc HCl (20 mL). The product was filtered off, washed with H_2O, dried and recrystallized.

Method 16. N,N-Diethyl-1-[2-(4-chlorophenyl)-1-methyl-5-1H-benzimidazolyl]ethanamine ***38***
The chlorocompound **76** (9.58 g, 87.8% pure, 0.025 mol) in dry C_6H_5Me (26 mL) was stirred and treated with $HNEt_2$ (18.29 g, 26.12 mL, 0.25 mol) at room temperature. The mixture was stirred at 87 °C for 16.5 h. The cooled C_6H_5Me was extracted with 2 N HCl. The acid solution was basified with 50% aq NaOH solution to give a gum which was extracted with CH_2Cl_2. The CH_2Cl_2 yielded the free base which was converted to its hydrochloride by dissolving in MeOH and adding HCl gas. The solid was filtered off and using aq NH_3 (d = 0.88) converted to the free base, which was recrystallized.

Method 17. 1-Acetylamino-1-[2-(4-chlorophenyl)-1-methyl-5-1H-benzimidazolyl]ethane ***40***
The oxime **37** (19.8 g, 0.066 mol) was hydrogenated in AcOH (50 mL) and Ac_2O (50 mL) in a Parr apparatus at 44 psi with

PtO_2 (1 g). After removal of catalyst the solution was treated with H_2O (100 mL) and extracted with Et_2O (2 × 100 mL). The Et_2O was washed with saturated aq $NaHCO_3$ (2 × 20 mL) and H_2O (20 mL). The combined aq phases were adjusted to pH 6 by adding sat aq $NaHCO_3$ (150 mL) and extracted with EtOAc (2 × 100 mL). The product, crystallized in the EtOAc, was filtered off and recrystallized.

Method 18. 1-(3-Aminopropyl)-1H-benzimidazole, maleate salt ***41***
EtOH (80 mL), saturated with NH_3, was added to Raney Ni W2 catalyst (2–3 mL of suspension). 1H-benzimidazole-1-propanenitrile [13] (8.3 g, 0.0485 mol) was then added and the mixture was hydrogenated in a Parr apparatus at 60 psi at room temperature. The mixture was filtered through Supercel, evaporated at 50 °C/vac to give a light brown liquid which was treated with a warm solution of maleic acid (5.63 g, 0.0485 mol) in EtOH (15 mL) and refrigerated. The resulting product was recrystallized.

Method 19. 2-(4-Chlorophenyl)-1-(2-hydroxyethyl)-6-chloro-1H-benzimidazole ***42***
The aminoalcohol **78** (6.38 g, 0.034 mol) and 4-chlorobenzaldehyde (4.8 g, 0.034 mol) in $C_6H_5NO_2$ (41 mL) were refluxed for 0.5 h and refrigerated for 2 days. The product was treated with light petroleum (bp 60–80 °C), filtered, washed with petroleum and dried at 40 °C/10 mmHg. The product was then recrystallized. In some cases the required diamine was produced by hydrogenation of the nitro compound in EtOH and then refluxed with the aldehyde in EtOH, before removal of EtOH and reaction in $C_6H_5NO_2$, eg, **54**, **55**.

Method 20. 2-(4-Chlorophenyl)-1-phenyl-6-chloro-1H-benzimidazole ***43***
5-Chloro-2-nitrodiphenylamine [14] (24.87 g, 0.1 mol) in EtOH (250 mL) was hydrogenated over PtO_2 (0.5 g) in a Parr apparatus at 61 psi for 2.25 h. The solution was filtered through Supercel into a suspension of 4-chlorobenzaldehyde (14.06 g, 0.1 mol) in EtOH (500 mL) and the mixture refluxed under N_2 for 2.5 h. After leaving overnight at room temperature no aldehyde was detectable by TLC so $FeCl_3$ (32.44 g, 0.2 mol) in EtOH was added and the reaction was refluxed for 6.5 h. Further $FeCl_3$ was added and refluxed for a further 6 h. The solution was evaporated to dryness, treated with H_2O (200 mL) and extracted four times with $CHCl_3$. Evaporation of the solvent gave the product which was recrystallized.

Method 21. 2-(4-Chlorophenyl)-1-phenyl-6-N-n-butyl-N-(2-methyl)ethanoyl-1H-benzimidazole ***56***
The amine **55** (3 g, 0.008 mol) and *iso*-butyric anhydride (19 g, 0.12 mol) were refluxed for 5 h, and poured into sat $NaHCO_3$ (100 mL) to give a gummy solid which was separated and evaporated to dryness and distilled to give the product.

Method 22. 2-(4-Chlorophenyl)-α-oxo-1-phenyl-1H-benzimidazole-5-acetaldehyde, oxime ***60***
A solution of compound **58** (10.4 g, 0.03 mol) in DMSO (100 mL) containing *tert*-butylnitrite (3.4 g, 0.033 mol) was added with stirring over 10 min to a solution of Na (0.828 g, 0.036 mol) in a mixture of *t*-BuOH (30 mL) and DMSO (30 mL) so that, with ice-bath cooling, the temperature remained at 20 °C. The solution was kept at room temperature for 48 h, treated with AcOH (2.05 mL, 0.035 mol) and poured into H_2O (400 mL) to give the product, which was recrystallized.

Method 23. 2-(4-Chlorophenyl)-α-methyl-1-phenyl-1H-benzimidazole-5-methanamine maleate salt ***61***
Compound **58** (4 g, 0.0115 mol) was refluxed for 10 h in $HCONH_2$ (6.8 g, 6.07 mL, 0.153 mol) and 90% HCO_2H (1.14 mL). Further quantities of HCO_2H (1 mL at a time, total 6 mL) were added when NH_3 was detectable above the mixture. Conc HCl (10 mL) was added and the mixture refluxed for 2 h. It was poured into 30% NaOH solution (30 mL), extracted with CH_2Cl_2 (five times), the CH_2Cl_2 dried (Na_2SO_4), filtered and evaporated to give a solid (3.4 g). This (2 g) was dissolved in hot EtOH (10 mL) and treated with maleic acid (0.68 g) in hot EtOH (11 mL). Crystallization gave the product.

Method 24. 2-[1-[2-(4-Chlorophenyl)-1-phenyl-1H-benzimidazol-5-yl]ethylidene]hydrazine carboxamide ***63***
The ketone **58** (4 g, 0.0115 mol) was refluxed in EtOH (100 mL) with AcONa (1.89 g, 0.023 mol) and $H_2NNHCONH_2{\cdot}HCl$ (1.86 g, 0.0115 mol) for 3 h. The mixture was evaporated to dryness, treated and the product filtered off.

Method 25. 5-[2-(4-Chlorophenyl)-1-phenyl-1H-benzimidazol-5-yl]-5-methyl-2,4-imidazolidinedione ***64***
The ketone **58** (13.87 g, 0.04 mol) in DMF (200 mL) and H_2O (50 mL) containing KCN (5.2 g, 0.08 mol) and ammonium carbonate (24.44 g, 0.16 mol) was stirred and heated at 65–70 °C for 7 days. Further amounts (12 g) of ammonium carbonate were added after 5, 6 and 6.5 days until the ketone could not be detected by TLC. The mixture was evaporated to dryness, treated with H_2O, filtered, dried (40 °C/vac) and recrystallized.

Method 26. (E)/(Z)-1-[2-(4-Chlorophenyl)-1-phenyl-1H-benzimidazol-5-yl]-3-phenyl-2-propen-1-one ***65***
The ketone **58** (5 g, 0.014 mol) dissolved in EtOH (140 mL) with warming was cooled to 30 °C and treated with C_6H_5CHO (1.48 g, 1.41 mL, 0.014 mol) and NaOH (0.72 g, 0.018 mol) in H_2O (6.5 mL), stirred for 2.5 h and kept at room temperature overnight. The product was filtered off and recrystallized.

Method 27. 2-(5-Ethylpyridin-2-yl)benzimidazole ***70***
A mixture of *o*-phenylenediamine (15 g, 0.14 mol), 2-methyl-5-ethylpyridine (16.97 g, 0.14 mol) and S (13.5 g, 0.42 mol) was heated under N_2 with stirring at 160 °C for 7 h. After leaving at ambient temperature overnight it was treated with MeOH (200 mL), stirred and filtered to remove S. The filtrate was evaporated under vacuo to give the product.

Method 28. 3-Amino-4-(4-chlorobenzamido)anisole ***73***
(i) 4-Methoxy-2-nitroaniline (8.41 g, 0.05 mol) suspended in pyridine (17.5 mL) was stirred and 4-chlorobenzoyl chloride (8.75 g, 6.35 mL, 0.05 mol) was added over 7 min. The temperature rose to 67 °C. The mixture was kept at ambient temperature for 21.5 h and stirred at 88 °C for 1 h. It was cooled to 40 °C and added to H_2O (175 mL) and the product 4-(4-chlorobenzamido)-3-nitroanisole (14.3 g), mp 155 °C [Anal ($C_{14}H_{11}ClN_2O_4$) C, H, N] was filtered off and dried at 47 °C/vac. (ii) The above nitro compound (60.4 g, 0.197 mol) in dioxan (250 mL) was hydrogenated over 10% Pd/C (5 g) in a Parr apparatus at 66 psi. After filtration of the catalyst the filtrate was diluted with H_2O (3 L) to yield **73**, which was dried at 45 °C/vac.

Method 29. 3-Amino-2-[N-(4-chlorobenzoyl)-N-methyl]aminophenetole ***74***
(i) 2,3-Dinitrophenetole [16] (6.8 g, 0.032 mol) was stirred in DMF (27 mL) and treated with 33% $MeNH_2$ in EtOH

(16.3 mL, 0.16 mol) and kept at ambient temperature for 65 h. The solution was poured into H_2O (1250 mL), extracted with EtOAc (4 × 500 mL), dried ($MgSO_4$), filtered and the solvent evaporated in vacuo to give 2-*N*-methylamino-3-nitrophenetole as an impure crystalline solid (5.96 g) mp 45–52 °C. (ii) The product from (i) (22.72 g, 0.115 mol) was treated with 4-chlorobenzoyl chloride (11.15 g, 0.064 mol) and pyridine (45 mL) as in method 28(i) to give 2-[*N*-(4-chlorobenzoyl)-*N*-methyl]-amino-3-nitrophenetole (18.97 g), mp 104 °C. (iii) **74** was obtained by hydrogenation of the latter compound as in method 28(ii).

Method 30. 3-Amino-4-[N-(4-chlorobenzoyl)-N-methyl]amino-anisole 75
(i) 4-Amino-3-nitroanisole (50 g, 0.295 mol) in CF_3CO_2H (130 mL) was stirred and treated with $(CF_3CO)_2O$ (250 g, 167 mL, 1.19 mol) dropwise over 30 min. It was kept at ambient temperature for 96 h, and poured into H_2O (1.5 L). The resulting 4-methoxy-2-nitrotrifluoroacetanilide (76.1 g), mp 95 °C [$C_9H_7F_3N_2O_4$ (C, H, N)], was filtered, washed and dried in vacuo. (ii) Crushed NaOH (24 g, 0.6 mol) was added to a solution of the above anilide (39.6 g, 0.15 mol) and MeI (85.2 g, 0.6 mol, 3.75 mL) in dry $COMe_2$ (750 mL). This was stirred and refluxed for 10 min, and evaporated to dryness in vacuo. This was treated with H_2O (750 mL), stirred and refluxed for 0.5 h and then stirred at ambient temperature for 1 h. The resulting 4-methylamino-3-nitroanisole (25.58 g), mp 98–100 °C [($C_8H_{10}N_2O_3$) C, H, N] was filtered, washed with H_2O, and dried in vacuo. (iii) The product from (ii) (20 g, 0.11 mol) was treated with 4-chlorobenzoyl chloride (23.1 g, 16.8 mL, 0.132 mol) and pyridine (80 mL) as in method 28(i) to give 4-(*N*-chlorobenzoyl-*N*-methyl)amino-3-nitroanisole (35.2 g), mp 77–79 °C, ($C_{15}H_{13}ClN_2O_4$) C, H, N. (iv) **75** was obtained by hydrogenation of the previous compound as in method 28(ii).

Method 31. 2-(4-Chlorophenyl)-5-(1-chloroethyl)-1-methyl-1H-benzimidazole 76
The alcohol **35** (17.9 g, 0.062 mol), suspended in CH_2Cl_2 (179 mL), was treated with $SOCl_2$ (36.9 g, 22.5 mL, 0.31 mol) over 2 min. After the frothing had died down the solution was kept at ambient temperature for 20 min, evaporated in vacuo at 50 °C, CH_2Cl_2 (50 mL) was added, the solution was evaporated and the process repeated to yield impure **76** (21 g) as a white solid foam.

Method 32. 2-[2-(Amino-5-chlorophenyl)amino]ethanol 78
(i) 3,4-Dinitrochlorobenzene (50 g, 0.25 mol) in EtOH (200 mL) was treated with 2-aminoethanol (31 g, 0.5 mol) in EtOH (100 mL) and refluxed for 2 h (cf [14]). After keeping at ambient temperature for 48 h the solution was treated with conc aq NH_3 and H_2O and cooled in ice to give 2-[(5-chloro-2-nitro)phenylamino]ethanol as a red solid (26.17 g), mp 118 °C ($C_8H_9ClN_2O_3$) C, H, Cl, N. (ii) The above nitro compound (12 g, 0.053 mol) and Sn (35.7 g, 0.3 g atom) were mixed and treated with cooling with conc HCl (70.4 mL). The colourless solution was heated at 100 °C for 1 h, then diluted with H_2O (100 mL) to precipitate a white solid. This was added to a solution of NaOH (75 g, 1.875 mol) in H_2O (500 mL) containing ice. The white solid dissolved and then **78** precipitated. It was collected and dried in vacuo to give **78**, mp 102 °C.

Method 33. 4-(2-Hydroxyethyl)-2-phenylaminoaniline 79
(i) 5-Chloro-2-nitrodiphenylamine [14] (4.9 g, 0.0197 mol), 2-hydroxyethylamine (2.43 g, 2.4 mL, 0.04 mol), K_2CO_3 (2.76 g, 0.02 mol) and KBr (100 mg) were stirred at 100 °C overnight. The mixture was poured into H_2O (300 mL) and extracted with $CHCl_3$. This was washed with saturated NaCl solution, dried ($MgSO_4$), filtered and evaporated to give the product as an oil, which crystallized from EtOH to give 4-(2-hydroxyethyl)-2-phenylaminonitrobenzene (2.78 g), mp 104 °C ($C_{14}H_{15}N_3O_3$) C, H, N. (ii) The above compound was hydrogenated in EtOH (cf method 11) to give **79** and the solution of **79** was used to react with 4-ClC_6HCHO (cf method 20). After evaporation of the EtOH, the reaction was completed (cf method 19), to give compound **54**.

Method 34. 4-n-Butylamino-2-phenylaminoaniline 80
(i) 4-*n*-Butylaminonitrobenzene (84% yield), mp 87 °C [($C_{16}H_{19}N_3O_2$) C, H, N] was produced by method 33(i). (ii) Using method 33(ii) the latter nitrocompound was converted first to compound **80** and then to compound **55**.

Method 35. 4-1H-Imidazolyl-2-phenylaminoaniline 81
4-1*H*-Imidazolyl-2-phenylaminonitrobenzene (58% yield), mp 160–161 °C [($C_{15}H_{12}N_4O_2$) C, H, N] was obtained by method 33(i). (ii) The latter compound was converted to compound **81** and from this to compound **57** by means of method 33(ii).

Biological methods

Adjuvant arthritis
Female Sprague–Dawley rats were used in groups of six. Arthritis was induced and assessed by the method previously described [7]. The effects of dosing compounds **1–72** (tables I and II) were investigated and the result obtained for active compounds are recorded in table IV.

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